Complementary and alternative medicine use in glioma patients in France

Le Rhun, Emilie ; Devos, Patrick ; Bourg, Véronique ; Darlix, Amélie ; Lorgis, Véronique ; Ahle, Guido ; Boone, Mathieu ; Taillandier, Luc ; Curtit, Elsa ; Gras, Louis ; Lebrun Frenay, Christine ; Gramatzki, Dorothee ; Ramirez, Carole ; Simon, Nicolas ; Weller, Michael

Abstract: PURPOSE Complementary and alternative medicine (CAM) use increases in cancer patients, including adult patients with diffuse gliomas. METHODS Questionnaires addressing CAM use were distributed to adult patients with gliomas of WHO grades II-IV and ECOG performance score of 0-2 during hospital visits and filled in anonymously. The study was conducted in nine centers in France from May 2017 to May 2018. Descriptive cohort analyses and comparative analyses according to gender, age, WHO grade, and recurrent versus newly diagnosed disease were conducted. RESULTS Two hundred twenty-seven questionnaires were collected; 135 patients (59%) were male. Median age was 48 years, 105 patients (46%) declared having glioblastoma, 99 patients (43%) declared having recurrent disease. Hundred-three patients (45%) had modified their alimentary habits after the glioma diagnosis. At the time of the questionnaire, 100 patients (44%) were on complementary treatment, mainly vitamins and food supplements, and 73 patients (32%) used alternative medicine approaches, mainly magnetism and acupuncture. In total, 154 patients (68%) declared using at least one of these approaches. Expenditures exceeding 100 € per month were reported by users in 14% for modification of alimentary habits, in 25% for complementary treatment, and in 18% for alternative medicines. All approaches were commonly considered as improving quality of life and experienced as efficient, notably those associated with more expenditures. CONCLUSIONS CAM are frequently used by glioma patients in France. Underlying needs and expectations, as well as potential interactions with tumor-specific treatments, and financial and quality of life burden, should be discussed with patients and caregivers.

DOI: https://doi.org/10.1007/s11060-019-03315-8

Journal of Neuro-Oncology

Complementary and alternative medicine use in glioma patients in France

--Manuscript Draft--

Manuscript Number:	NEON-D-19-00602R1
Full Title:	Complementary and alternative medicine use in glioma patients in France
Article Type:	Clinical Study
Keywords:	acupuncture; Brain; diet; magnetism; supplements; vitamins
Corresponding Author:	Emilie Le Rhun, MD Lille LILLE, FRANCE
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	Lille
Corresponding Author's Secondary Institution:	
First Author:	Emilie Le Rhun, MD
First Author Secondary Information:	
Order of Authors:	Emilie Le Rhun, MD
	Patrick Devos
	Veronique Bourg
	Amelie Darlix
	Veronique Lorgis
	Guido Ahle
	Mathieu Boone
	Luc Taillandier
	Elsa Curtit
	Louis Gras
	Christine Lebrun-Frenay
	Dorothee Gramatzki
	Carole Ramirez
	Nicolas Simon
	Michael Weller
Order of Authors Secondary Information:	
Funding Information:	
Abstract:	Purpose: Complementary and alternative medicine (CAM) use increases in cancer patients, including adult patients with diffuse gliomas. Methods: Questionnaires addressing CAM use were distributed to adult patients with gliomas of WHO grades II-IV and ECOG performance score of 0-2 during hospital visits and filled in anonymously. The study was conducted in nine centers in France from May 2017 to May 2018. Descriptive cohort analyses and comparative analyses according to gender, age, WHO grade, and recurrent versus newly diagnosed disease were conducted. Results: Two hundred twenty-seven questionnaires were collected; 135 patients (59%) were male. Median age was 48 years, 105 patients (46%) declared having glioblastoma, 99 patients (43%) declared having recurrent disease. Hundred-three

	patients (45%) had modified their alimentary habits after the glioma diagnosis. At the time of the questionnaire, 100 patients (44%) were on complementary treatment, mainly vitamins and food supplements, and 73 patients (32%) used alternative medicine approaches, mainly magnetism and acupuncture. In total, 154 patients (68%) declared using at least one of these approaches. Expenditures exceeding 100 € per month were reported by users in 14% for modification of alimentary habits, in 25% for complementary treatment, and in 18% for alternative medicines. All approaches were commonly considered as improving quality of life and experienced as efficient, notably those associated with more expenditures. Conclusions: CAM are frequently used by glioma patients in France. Underlying needs and expectations, as well as potential interactions with tumor-specific treatments, and financial and quality of life burden, should be discussed with patients and caregivers.

RESPONSE TO REFEREES

Reviewer #1: The present study addresses the use of alternative medicine in glioma patients. Although several studies addressed the particular topic before, this the first to specifically address patients in France. Although certainly interesting and import the study would profit from some improvement. In the discussion the authors should put their data a little bit more into context with the previous studies addressing the same issue in other European countries - what is different and potentially special to the French population.

RESPONSE
We have inserted some considerations on the specificities of France (page 10 and page 11, in the "Discussion" paragraph.

Some further points:

COMMENT
Is it possible to include the time since diagnosis?

RESPONSE
These data have been added (see page 6, in the "Patient characteristics" paragraph and in table 1).

COMMENT
A translated version of the entire questionnaire should be given in the supplementary material.

RESPONSE
This is what Supplementary Table 1 shows. May be this was overlooked.

COMMENT
Introduction: Gliomas represent the main primary brain tumors in adults.
- what do you mean by "main"? The most frequent?

RESPONSE
This has been corrected in the text, page 4.

COMMENT
Was there a minimum of required fields to be addressed so the questionnaire was included in the analysis? Information should be provided on how many participants did not answer particular field. Was the analysis than performed only included the questionnaires with answers? Would that mean a potential bias?

RESPONSE
The questionnaires were distributed to patients that were volunteers to fill it anonymously. All questionnaires were taken into account and included in the analyses; 219 participants answered regarding smoking and alcohol habits, alimentation and diet, 224 participants regarding complementary treatment use, and 217 regarding alternative treatment use. This has been more clearly indicated in the revised tables.

COMMENT
First line therapy a little odd with 46% glioblastoma and only 13% receiving concomitant treatment?

RESPONSE

We agree with this comment. This is unlikely to be correct, but illustrates the limitations of a questionnaire. We have specifically commented on this (see page 13, in the "Discussion" paragraph).

COMMENT
Which patients were addressed? Is there a potential inclusion bias?

RESPONSE

The questionnaire was distributed to all glioma patients seen from May 2017 to May 2018, with an ECOG performance score of 0-2, as stated in the Methods section (Methods, page 5). Inclusion criteria were provided to all centers and investigators. The answers provided here correspond to declaration of participants only. Please see comment in the limitations section (page 13).

COMMENT
How many received information on complementary therapy from oncologist?

RESPONSE
This information is given in Tables 3 to 5 (13% among participants who have declared a modification of alimentary habits or being under diet; 15% among patients who have declared complementary treatment consumption and 7% among patients who have declared alternative treatment use).

COMMENT
figure displaying the rated impact and efficacy of the used methods is enough - would omit the description of Figure 1 in the text
- Figure 1 - what is the y axis? % of patients?
- Total number of patients included in the particular analysis should be given

RESPONSE
We apologize for omitting the legend for the Y-axis – the referee is correct (this has been fixed). Total number of patients included are now provided in the figure legend. The figure is described only with one sentence each for panels A/B, C/D and E/F. The percentages of patients have been modified for clarity and take into account now only patients who declared CAM use.

COMMENT
Correlation of impact on quality of life/ efficacy and cost should be described also giving numbers - correlation coefficient - page 8 2nd paragraph

RESPONSE
We feel that we should not apply too complicated statistics here since these are entirely explorative considerations without a predefined analysis plan and since we have only small subgroups of patients (0-30) in each category. As proposed elsewhere, we have reduced the numbers in the text.

COMMENT
Where there patients with multiple CAM use? Alternative treatment in addition to food changes?

RESPONSE
We thank the reviewer for this interesting point. We have added this information (see pages 6-7, in the "Pattern of CAM use" paragraph).

COMMENT
What is diagnosis "other"?

RESPONSE
Other refers to other brain tumors according to the patients. Patients declared having a medulloblastoma (n=3), meningioma (n=1), hemangiopericytoma (n=1), hemangioblastoma (n=1), or meningioma/schwannoma in the context of neurofibromatosis (n=1). This has been clarified as a footnote to Table 1.

COMMENT
Did all patients indicating to used CAM also indicate the efficacy and impact on quality of life?

RESPONSE
This has been clarified in the tables. For clarity, only patients that declared CAM use have been now taken into account when showing the percentages in the revised tables.

COMMENT
Consider to shorten the results and to not repeat too many numbers also given in the tables.

RESPONSE

The results have been condensed.

COMMENT
Consider to shorten the discussion

RESPONSE
The discussion has been condensed.

COMMENT
No numbers should be given in the discussion

RESPONSE
This has been revised.

COMMENT
Data on the association of Glioma grade and CAM use should be included in the main document - was is association also explored in the previous studies or is this a new finding? Why are GBM patients more interested in CAM?

RESPONSE
These data have been shifted to the main text. We have also expressed our interpretation that glioblastoma patients are more desperate and therefore more likely to seek alternative treatment options (see page 10, in the "Discussion" paragraph).

COMMENT
Page 10 line 34 to 41 - consider to make 2 sentences

RESPONSE
This has been done.

COMMENT
Which data supports the safety of CAM especially in combination with treatment in glioma patients - is there a study supporting this notion on page 11 line 32

RESPONSE
This is an (our) assumption, but this was never formally tested. We modified the text accordingly (page 12, in the "Discussion" paragraph).

Reviewer #3: This is an interesting study on the use of complementary and alternative medicine use in glioma patients in France.
It is a retrospective study using surveys with its known limitations, but for the rest the study is well-performed and well-written.

I have some comments.

COMMENT
1. Did the patients experience negative effects of the CAM? And did the authors ask also whether CAM had a negative impact on quality of life?

RESPONSE
The questionnaire was as shown in Table S1. The participants could indicate on a scale from 1 (bad) to 10 (good) how CAM affected their quality of life. The corresponding data are summarized in Tables 3-5.

COMMENT
2. There was a high no-response rate for impact on quality of life, efficacy and estimation of cost per month (59-68%). Can the others explain this high no response rate?
What is the impact of this high no response rate on the interpretation of the data? Do the authors think that these patients that experience a low quality of life or no efficacy did not respond. Please discuss.

RESPONSE

We are thankful for this comment because it made clear that our data presentation was not clear enough. Percentages now are exactly explained and “no response” figures are given in Tables 3-5. Regarding the “no “response” rates that remain, we prefer not to speculate too much whether non-responders had less favorable experiences with CAM use. It can also not be excluded that some questions were too complicated for some patients. We have included considerations on this topic (see page 13, in the "Discussion" paragraph).

COMMENT
3. page 35: cost or reimbursement was less important in the decision making in Germany and Switzerland. Compared to which other countries?

RESPONSE
The sentence has been modified.

NEON-S-19-00974 - Journal of Neuro-Oncology

Complementary and alternative medicine use in glioma patients in France

Emilie Le Rhun[1,2,3,4,5], Patrick Devos[6], Véronique Bourg[7], Amélie Darlix[8], Véronique Lorgis[9], Guido Ahle[10], Mathieu Boone[11], Luc Taillandier[12], Elsa Curtit[13], Louis Gras[14], Christine Lebrun Frenay[7], Dorothee Gramatzki[5], Carole Ramirez[3], Nicolas Simon[15], Michael Weller[5]

1 University of Lille, U-1192, F-59000 Lille, France
2 Inserm, U-1192, F-59000 Lille, France
3 CHU Lille, General and Stereotaxic Neurosurgery Service, F-59000 Lille, France
4 Oscar Lambret Center, F-59000 Lille, France
5 Department of Neurology, University Hospital and University of Zurich, Zurich, Switzerland
6 University of Lille, CHU Lille, EA 2694 - Santé publique : épidémiologie et qualité des soins, F-59000 Lille, France
7 CRCSEP Neurology, Pasteur2 Hospital. Nice Côte d'Azur University, Nice, France
8 Department of Medical Oncology, Institut du Cancer de Montpellier, University of Montpellier, Montpellier, France
9 Georges François Leclerc, Anticancer Center, Dijon, France
10 General Hospital, Colmar, France
11 University Hospital, Amiens, France
12 University Hospital, Nancy, France
13 University Hospital, Besançon, France
14 Centre Léonard de Vinci, Dechy, France
15 Univ. Lille, CHU Lille, EA 7365 – GRITA – Groupe de Recherche sur les Formes Injectables et les Technologies Associées, Lille, France.

Corresponding author
Emilie Le Rhun, MD, PhD, Neuro-oncology, Neurosurgery Department, Roger Salengro Hospital, Rue Emile Laine, University Hospital CHRU, 59037 Lille cedex, France
Phone: +33.3.20.44.59.62
email: emilie.lerhun@chru-lille.fr

Running title
Complementary and alternative medicine use in glioma patients

Word count
Abstract word count: 250, text word count: 2787, number of references: 36, number of tables/figures: 5

Abstract

Purpose: Complementary and alternative medicine (CAM) use increases in cancer patients, including adult patients with diffuse gliomas.

Methods: Questionnaires addressing CAM use were distributed to adult patients with gliomas of WHO grades II-IV and ECOG performance score of 0-2 during hospital visits and filled in anonymously. The study was conducted in nine centers in France from May 2017 to May 2018. Descriptive cohort analyses and comparative analyses according to gender, age, WHO grade, and recurrent versus newly diagnosed disease were conducted.

Results: Two hundred twenty-seven questionnaires were collected; 135 patients (59%) were male. Median age was 48 years, 105 patients (46%) declared having glioblastoma, 99 patients (43%) declared having recurrent disease. Hundred-three patients (45%) had modified their alimentary habits after the glioma diagnosis. At the time of the questionnaire, 100 patients (44%) were on complementary treatment, mainly vitamins and food supplements, and 73 patients (32%) used alternative medicine approaches, mainly magnetism and acupuncture. In total, 154 patients (68%) declared using at least one of these approaches. Expenditures exceeding 100 € per month were reported by users in 14% for modification of alimentary habits, in 25% for complementary treatment, and in 18% for alternative medicines. All approaches were commonly considered as improving quality of life and experienced as efficient, notably those associated with more expenditures.

Conclusions: CAM are frequently used by glioma patients in France. Underlying needs and expectations, as well as potential interactions with tumor-specific treatments, and financial and quality of life burden, should be discussed with patients and caregivers.

Key words: acupuncture, brain, diet, magnetism, supplements, vitamins

Text

Introduction

Complementary and alternative medicine (CAM) is operationally defined as any practice that aims at cure or at obtaining similar effects as evidence-based medicine, but without scientific evidence and without clinical trial data to support efficacy and safety. Some approaches have been integrated into standards of care on a regional level, others have been explored in trials, some are toxic or violate local laws. However, CAM is frequently and probably increasingly used in cancer patients [1]. CAM is also sometimes denoted as complementary and alternative practices and products (CAPP), complementary and integrative medicine (CIM), complementary medicine (CM), complementary and traditional medicine or complementary health approaches (CHA). It can include pharmacological-like therapies, diets, modification of alimentation, food supplements, mind-body interventions, and others. No widely accepted consensual international definition of CAM is available, rendering comparisons across studies from different countries and periods difficult. By default, CAM represent approaches that are outside of the "mainstream medical model" [2]. The Cochrane group has defined CAM as " therapies used in treating or preventing disease" and has identified 70 different terms or combination of terms. Supplements administered parenterally at hospital, supplements for treatment or prevention of

medically diagnosed deficiency states and disorders, vitamins used for prevention of treatment effects, and exercise therapy are not considered as CAM [2].

Second to meningiomas gliomas represent the most common primary brain tumors in adults. Their prognosis varies by WHO grade and molecular subtype, available treatments, and the patients' general and neurological condition. Glioblastoma, the most malignant subtype of glioma (WHO grade IV), accounts for 56.6% of all gliomas [3]. Median survival for patients with glioblastoma is in the range of 16 months in clinical studies [4-8], but remains at 12 months on a population level [9]. WHO grade II and III gliomas have a better prognosis with median survival times in clinical studies of up to 5 years for anaplastic gliomas without 1p19q codeletion and up to 14 years in the presence of 1p19q codeletion [10-12], and up to 13 years for molecularly unselected "high risk" WHO grade II glioma [13]. In this context of severe illness and limited efficacy of evidence based-medicine, patients and relatives may more often resort to CAM.

The present study was conducted to explore CAM use in adult glioma patients in France, to determine whether CAM use may affect quality of life, familial organization, leisure activities and to estimate the cost and the financial consequences of different CAM approaches, with the goal to better understand needs, motivations and expectations of patients and their caregivers.

Methods

We conducted a prospective multi-center study in 9 French centers within the North East Neuro-Oncology (NENO) network. From May 2017 to May 2018 adult patients with histologically confirmed diffuse glioma of WHO grades II-IV and an ECOG performance score of 0-2 were asked to fill out a questionnaire anonymously at any time during the course of disease. The questionnaire was designed by ELR in cooperation with NS and approved by all participating sites. The questionnaires were distributed during hospital visits and completed during the same appointment. They included four different parts: (1) patient and tumor characteristics, including treatment received for the glioma, (2) modification of alimentation habits, (3) complementary treatments and (4) alternative medicine/traditional medicine use. An English version of the questionnaire is shown in Table S1. Patients were asked to grade the efficacy of such therapies and their impact on their own quality of life on a numerical analog scale from 1 (lowest) to 10 (highest). In addition, we interrogated source of information on CAM, perceived impact on quality of life, perceived efficacy, estimated cost per month (in €), and impact on familial life, leisure activities, and finances. All returned questionnaires were included in the analysis.

Descriptive analyses of the population as well as comparative analyses according to gender, age, WHO grade (IV versus other WHO grades), and recurrent disease versus newly diagnosed setting were conducted using the Chi-square test. Only patients who declared using the respective CAM were included in the descriptive analyses of CAM consumption.

A level of significance of 5% was used. Analyses were performed with SAS V9.4 and SPSS 22. The project was approved by the French authorities (CCTIRS 16-218, MR-003 -108).

Results

Patient characteristics

Two hundred twenty-seven anonymous questionnaires were filled in between May 15, 2017 and May 31, 2018. Hundred thirty-five participants declared to be male (59%) and 79 patients declared to be female (35%). Median age was 48 years. The diagnoses were WHO grade II glioma in 29%, grade III glioma in 16% and glioblastoma (grade IV) in 46%. Beyond surgery, patients reported as first-line treatment radiotherapy alone in 5 cases (2%), chemotherapy alone in 131 cases (58%), and their combination in 31 cases (14%). Ninety-nine patients (43%) had experienced recurrence (Table S2). The median interval between diagnosis and questionnaire completion was declared to be 20 months.

Patterns of CAM use

Hundred-three patients (45%) declared having modified their alimentary habits, 100 patients (44%) were on complementary treatment, and 73 patients (32%) used alternative medicine approaches; 154 patients (68%) declared using at least one of these approaches. Sixty-seven patients (29%) declared having changed their alimentation habits and taking complementary treatment, 46 patients (20%) declared having changed their alimentation habits and using alternative therapy, and 48 patients (21%) declared using both complementary treatment and alternative therapy. Thirty-five patients (15%) used CAM from all three categories.

Among patients who answered to the question, a modification of familial organization in response to CAM use was reported by 18% to 28% of the patients, most often in

association with modification of alimentation and diets (Figure S1). An impact on leisure activities was reported by 8% to 17% of patients using CAM, and was mainly related to complementary treatment. Among patients who answered to the question, a financial impact was reported by 15% to 20% of patients, mostly reported by patients using complementary treatment (20%) and alternative therapies (17%). Glioblastoma patients as opposed to patients with other tumors used significantly more often at least one CAM approach. The difference was more prominent for modification of alimentary habits and use of complementary treatment than for use of alternative therapy. No association was found between gender, age, or recurrent disease and the use of one or these approaches (Table 1).

Smoking and alcohol habits, alimentation and diet

Thirty-five patients (15%) declared having modified their smoking habits since the diagnosis of the brain tumor, however, 57 patients (50%) reported ongoing consumption. Only 56 patients (25%) reported no current alcohol consumption. Hundred-three patients (45%) reported a modification of alimentary habits. More than 25% of the patients reported an increase in the consumption of green tea, curcuma, or lemon, and 27 patients (12%) followed a diet, including a ketogenic diet in 5 patients. Information on alimentation and diet was mainly received from relatives (26%), and less frequently from general practitioners (15%), oncologists (13%). The impact on quality of life of modified alimentation was estimated as good with a median of 7 on the scale from 1 (lowest) to 10 (highest). Thirty-eight patients (35%) rated the impact on quality of life at 4-7 and 35 patients (32%) at 8-10. Efficacy was also perceived as good, with a median of 7. Forty-two patients (39%) rated the efficacy at 4-7 and 36 patients (33%) at 8-10. Information on cost of modified

alimentation habits was provided by 63 patients (58%); it was estimated as less than 30 € per month by 35 patients (32%) and as more than 200 € per month by 10 patients (9%). Twenty-two patients (20%) declared that modifications of alimentation and diet had an impact on their familial organization, 12 patients (11%) on their leisure activities, and 12 patients (11%) on their finances (Table 2). Expenditures exceeding 200 € per month were not necessarily perceived as having more impact on quality of life and as more efficacious than expenditures of 200 € or less per month (Figure 1A,B).

Complementary treatment

Hundred participants (44%) declared having taken or taking complementary treatments, mainly vitamins (23%), food supplement (22%), phytotherapy (15%) or homeopathy (15%). Information on complementary treatment was mainly received from relatives (30%) or general practitioners (29%). The impact on quality of life was judged as good and efficient, with a median of 7 each. Fifty-five patients (55%) rated the impact on quality of life at 4-7 and 32 patients (32%) at 8-10. Forty patients (40%) rated efficacy at 4-7 and 37 patients (37%) at 8-10.

Information on cost of altered alimentation habits was provided by 84 patients (84%). Cost of less than 30 € per month was reported by 38 patients (38%) whereas 200 € or more per month were invested by 15 patients (15%). Seventeen patients (17%) declared that the complementary treatment had an impact on their familial organization, 16 patients (16%) on their leisure, and 18 patients (18%) on their finances (Table 3). No clear correlation was observed between cost and quality of life or efficacy (Figure 1C,D).

Alternative treatment

Use of alternative treatment was reported by 73 patients (32%). Twenty-two patients (30%) declared to use mainly magnetism, 16 acupuncture (22%), 15 sophrology (21%) and 12 energizing therapy (16%). Information on these techniques was given mainly by relatives (58%). Patients estimated that the impact of alternative treatment on quality of life was good and that these approaches were efficient with a median score of 8. Twenty patients (10%) rated the impact on quality of life at 4-7 and 38 patients (19%) at 8-10. Twenty-three patients (31%) rated the efficacy at 4-7 and 38 patients (52%) at 8-10. Information on cost was provided by 63 patients (86%). It was declared as below 30 € per month by 22 patients (30%) and as more than 200 € per month by 6 patients (8%). An impact on familial organization was declared by 12 participants (16%), on leisure activities by 5 patients (7%) and on finances by 11 patients (15%) (Table 4). Alternative therapies received high ratings for impact on quality of life and efficacy even if not associated with high expenditures (Figure 1E,F).

Discussion

There is increased awareness of CAM use in general oncology. In a meta-analysis on studies involving more than 65,000 cancer patients in 18 countries conducted until January 2009, heterogeneity was observed that may have partially been related to differences between surveys. CAM use was estimated at 40%, with a clear increase in use over time: 25% in the 1970s and 1980s, more than 32% in the 1990s, and 49% after 2000 [1]. A rate of 66.5% of CAM users was reported among 1471 cancer

survivors in 2007 [14]. In another study, 720 questionnaires were collected between 2014 and 2016 in Germany. Here the rate of CAM use was 29% [15]. Specifically brain tumor patients may be interested in CAM because of perceived and factual shortcomings of available treatments. The present study is the first survey on CAM use by glioma patients conducted in France. It indicates widespread CAM use, with more than two thirds of participants declaring using at least one CAM approach. Information on CAM use was mainly received from family and friends (Tables 2-4). A positive impact on quality of life was commonly perceived, and efficacy was generally judged as good for all three CAM categories. A diagnosis of glioblastoma as opposed to lower WHO grade glioma was associated with more frequent CAM use, presumably because glioblastoma patients feel more need to fight their disease than patients with less malignant tumors (Table 1).

Previous contemporary studies have explored CAM use in glioma patient cohorts in the US and Canada [16-18], Germany [19] and Switzerland [20]. CAM use was in the range of 24% to 77%, partially because of differences in the definition of CAM [16-21] (Table S3). In these other cohorts, information on CAM was also mainly received by relatives or via internet, and a positive effect was generally perceived by CAM users [16-21]. In contrast to other reports, no association of CAM use with younger age [16-21] or female gender [17,19] was noticed in our survey. One might speculate that age loses significance as internet use as an important source of information becomes more prevalent among older patients, too. In our study, the cost per month was usually less than 50 €, in other studies, it was usually also estimated at inferior to 50 € or between 50 and 100 € [16,18,19]. The median annual cost for CAM users increased from 120 $AU in 1993 to 228 $AU in 2000 in Australia, with a median monthly cost of 19 $AU in 2000 [22].

The high consumption of CAM in the glioma patient population raises several important points, notable the impact on quality of life, its cost, the safety of agents, and potential interactions with cancer therapy. Most patients reported a positive impact of CAM use on quality of life. The impact on quality of life of CAM was previously evaluated using the Functional Assessment of Cancer Treatment–Brain (FACT–Br) questionnaire among 718 participants including 33% of CAM users [23]. The overall quality of life was not associated with CAM use, a lower emotional quality of life was associated with any CAM use and higher functional quality of life associated with body-oriented CAM use. Thus, objective evidence to support an impact of CAM on quality of life remains to be generated.

The quality of products and their safety should be discussed with patients. Mercury, lead and arsenic were analyzed in 193 Ayurvedic medicines purchased between August and October 2015 on a Website. The frequency of detection of metal was 20.7% among US-manufactured products versus 19.5% in products from India. Rasa shastra contained a greatest content of metals (p=0.007). Among products containing metal, 95% were available on US websites and 75% claimed "Good Manufacturing Practice" and all of them exceeded the acceptable standard for daily metal ingestion [24].

Few data are available on the toxicity of CAM. Most CAM are probably safe, however, minor but also major toxicities have been observed, such as hypersensitivity reactions, and neurological, cardiovascular, gastro-intestinal, renal and liver toxicities. Development of second cancer has also been linked to CAM use [25,26].

A possible interaction of the combination of conventional pharmacotherapy and pharmacologically based CAM methods has been reported in 54.9% of CAM users

[15], e.g., an induction of the cytochrome P450 enzyme system has been reported after using St. John's wort [27]. Accordingly, CAM use should be explored at the start of conventional pharmacotherapy to avoid pharmacokinetic or pharmacodynamic interactions.

Ketogenic or calorically restricted diets reduced tumor growth in preclinical studies [28,29]. The ERGO trial explored the feasibility of the ketogenic diet in 20 patients with recurrent glioblastoma. Among them, 3 (15%) discontinued the diet because of poor tolerability, and no clinical activity was noted [30]. No association between glioblastoma outcome and multivitamins or omega-3 fatty acids was observed in an exploratory analysis among 470 patients, but vitamin D users had a reduced mortality whereas vitamin E users had a non-significantly higher mortality [21].

A poor communication regarding CAM between patients and physicians has been reported [31]. Up to 74% of patients with cancer or specifically glioma declared that physicians were not informed of CAM use [18,32,33]. From the patient's perspective, the main causes making the communication between CAM users and physicians difficult are the lack of interest or the opposition of physicians, the lack of scientific evidence reported by the physicians and an anticipated negative response from the physicians [31,34]. The main motivation of glioma patients to use CAM was to contribute actively to the treatment, but not to question standard treatments. Cost or reimbursement was not important in the decision making in Germany and Switzerland [19,20].

Limitations of the present study include the limited number of patients for subgroups, the bias introduced by patient preferences to respond to the questionnaire or not, the lack of longitudinal data, and the inherent limitations of a survey without the option to verify information, e.g., the high rate or reporting chemotherapy only as first-line

treatment is highly unlikely to be correct. Furthermore, no data on safety were collected although a survey would probably be not the adequate tool to collect such data [35]. Future studies should prospectively address to what extent CAM use exerts intrinsic toxicity or alters tolerability and safety of standard cancer therapies or novel agents administered in the context of clinical trials [15]. As a prerequisite for that, it would be important to implement proper CAM use documentation in clinical patient records [36].

We conclude that there is high prevalence of CAM use among adult glioma patients in France. These should be interrogated and discussed with patients and caregivers during the course of the disease to identify patient needs and preferences as well as potential interactions with tumor-specific treatments.

Acknowledgements

The authors would like to thank Stéphanie Heudre for excellent administrational support.

References

1. Horneber M, Bueschel G, Dennert G, et al (2012) How many cancer patients use complementary and alternative medicine: a systematic review and metaanalysis. Integr Cancer Ther 11:187–203. https://doi.org/10.1177/1534735411423920
2. Wieland LS, Manheimer E, Berman BM (2011) Development and classification of an operational definition of complementary and alternative medicine for the Cochrane collaboration. Altern Ther Health Med 17:50–59
3. Ostrom QT, Gittleman H, Truitt G, et al (2018) CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2011-2015. Neuro-oncology 20:iv1–iv86. https://doi.org/10.1093/neuonc/noy131

4. Stupp R, Hegi ME, Mason WP, et al (2009) Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. Lancet Oncol 10:459–466. https://doi.org/10.1016/S1470-2045(09)70025-7
5. Chinot OL, Wick W, Mason W, et al (2014) Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma. N Engl J Med 370:709–722. https://doi.org/10.1056/NEJMoa1308345
6. Gilbert MR, Sulman EP, Mehta MP (2014) Bevacizumab for newly diagnosed glioblastoma. N Engl J Med 370:2048–2049. https://doi.org/10.1056/NEJMc1403303
7. Stupp R, Taillibert S, Kanner A, et al (2017) Effect of Tumor-Treating Fields Plus Maintenance Temozolomide vs Maintenance Temozolomide Alone on Survival in Patients With Glioblastoma: A Randomized Clinical Trial. JAMA 318:2306–2316. https://doi.org/10.1001/jama.2017.18718
8. Weller M, Butowski N, Tran DD, et al (2017) Rindopepimut with temozolomide for patients with newly diagnosed, EGFRvIII-expressing glioblastoma (ACT IV): a randomised, double-blind, international phase 3 trial. Lancet Oncol 18:1373–1385. https://doi.org/10.1016/S1470-2045(17)30517-X
9. Gramatzki D, Dehler S, Rushing EJ, et al (2016) Glioblastoma in the Canton of Zurich, Switzerland revisited: 2005 to 2009. Cancer 122:2206–2215. https://doi.org/10.1002/cncr.30023
10. van den Bent MJ, Brandes AA, Taphoorn MJB, et al (2013) Adjuvant procarbazine, lomustine, and vincristine chemotherapy in newly diagnosed anaplastic oligodendroglioma: long-term follow-up of EORTC brain tumor group study 26951. J Clin Oncol 31:344–350. https://doi.org/10.1200/JCO.2012.43.2229
11. Cairncross G, Wang M, Shaw E, et al (2013) Phase III trial of chemoradiotherapy for anaplastic oligodendroglioma: long-term results of RTOG 9402. J Clin Oncol 31:337–343. https://doi.org/10.1200/JCO.2012.43.2674
12. van den Bent MJ, Baumert B, Erridge SC, et al (2017) Interim results from the CATNON trial (EORTC study 26053-22054) of treatment with concurrent and adjuvant temozolomide for 1p/19q non-co-deleted anaplastic glioma: a phase 3, randomised, open-label intergroup study. Lancet. https://doi.org/10.1016/S0140-6736(17)31442-3
13. Buckner JC, Shaw EG, Pugh SL, et al (2016) Radiation plus Procarbazine, CCNU, and Vincristine in Low-Grade Glioma. N Engl J Med 374:1344–1355. https://doi.org/10.1056/NEJMoa1500925
14. Mao JJ, Palmer CS, Healy KE, et al (2011) Complementary and alternative medicine use among cancer survivors: a population-based study. J Cancer Surviv 5:8–17. https://doi.org/10.1007/s11764-010-0153-7
15. Firkins R, Eisfeld H, Keinki C, et al (2018) The use of complementary and alternative medicine by patients in routine care and the risk of interactions. J Cancer Res Clin Oncol 144:551–557. https://doi.org/10.1007/s00432-018-2587-7
16. Verhoef MJ, Hagen N, Pelletier G, Forsyth P (1999) Alternative therapy use in neurologic diseases: use in brain tumor patients. Neurology 52:617–622. https://doi.org/10.1212/wnl.52.3.617
17. Fox S, Laws ER, Anderson F, Farace E (2006) Complementary therapy use and quality of life in persons with high-grade gliomas. J Neurosci Nurs 38:212–220
18. Armstrong T, Cohen MZ, Hess KR, et al (2006) Complementary and alternative medicine use and quality of life in patients with primary brain tumors. J Pain Symptom Manage 32:148–154. https://doi.org/10.1016/j.jpainsymman.2006.02.015

19. Heese O, Schmidt M, Nickel S, et al (2010) Complementary therapy use in patients with glioma: an observational study. Neurology 75:2229–2235. https://doi.org/10.1212/WNL.0b013e31820202c6
20. Eisele G, Roelcke U, Conen K, et al (2019) Complementary and alternative medicine use by glioma patients in Switzerland. Neurooncol Pract 6:237–244. https://doi.org/10.1093/nop/npy035
21. Mulpur BH, Nabors LB, Thompson RC, et al (2015) Complementary therapy and survival in glioblastoma. Neurooncol Pract 2:122–126. https://doi.org/10.1093/nop/npv008
22. MacLennan AH, Wilson DH, Taylor AW (2002) The escalating cost and prevalence of alternative medicine. Prev Med 35:166–173
23. Mobed K, Liu R, Stewart S, et al (2009) Quality of Life and Patterns of Use of Complementary and Alternative Medicines Among Glioma Patients. J Support Oncol 7:W23–W31
24. Saper RB, Phillips RS, Sehgal A, et al (2008) Lead, mercury, and arsenic in US- and Indian-manufactured Ayurvedic medicines sold via the Internet. JAMA 300:915–923. https://doi.org/10.1001/jama.300.8.915
25. Markman M (2002) Safety issues in using complementary and alternative medicine. J Clin Oncol 20:39S-41S
26. Melchart D, Hager S, Albrecht S, et al (2017) Herbal Traditional Chinese Medicine and suspected liver injury: A prospective study. World J Hepatol 9:1141–1157. https://doi.org/10.4254/wjh.v9.i29.1141
27. Markowitz JS, Donovan JL, DeVane CL, et al (2003) Effect of St John's wort on drug metabolism by induction of cytochrome P450 3A4 enzyme. JAMA 290:1500–1504. https://doi.org/10.1001/jama.290.11.1500
28. Noorlag L, De Vos FY, Kok A, et al (2018) Treatment of malignant gliomas with ketogenic or caloric restricted diets: A systematic review of preclinical and early clinical studies. Clin Nutr. https://doi.org/10.1016/j.clnu.2018.10.024
29. Klement RJ, Bandyopadhyay PS, Champ CE, Walach H (2018) Application of Bayesian evidence synthesis to modelling the effect of ketogenic therapy on survival of high grade glioma patients. Theor Biol Med Model 15:12. https://doi.org/10.1186/s12976-018-0084-y
30. Rieger J, Bähr O, Maurer GD, et al (2014) ERGO: a pilot study of ketogenic diet in recurrent glioblastoma. Int J Oncol 44:1843–1852. https://doi.org/10.3892/ijo.2014.2382
31. Tasaki K, Maskarinec G, Shumay DM, et al (2002) Communication between physicians and cancer patients about complementary and alternative medicine: exploring patients' perspectives. Psychooncology 11:212–220. https://doi.org/10.1002/pon.552
32. Velicer CM, Ulrich CM (2008) Vitamin and mineral supplement use among US adults after cancer diagnosis: a systematic review. J Clin Oncol 26:665–673. https://doi.org/10.1200/JCO.2007.13.5905
33. Davis EL, Oh B, Butow PN, et al (2012) Cancer patient disclosure and patient-doctor communication of complementary and alternative medicine use: a systematic review. Oncologist 17:1475–1481. https://doi.org/10.1634/theoncologist.2012-0223
34. Richardson J (2004) What patients expect from complementary therapy: a qualitative study. Am J Public Health 94:1049–1053. https://doi.org/10.2105/ajph.94.6.1049
35. Stub T, Quandt SA, Arcury TA, et al (2016) Perception of risk and communication among conventional and complementary health care providers

involving cancer patients' use of complementary therapies: a literature review. BMC Complement Altern Med 16:353. https://doi.org/10.1186/s12906-016-1326-3
36. Stan DL, Wahner-Roedler DL, Yost KJ, et al (2018) Absent and Discordant Electronic Health Record Documentation of Complementary and Alternative Medicine in Cancer Care. J Altern Complement Med 24:988–995. https://doi.org/10.1089/acm.2018.0141

Figure legends

Figure 1. **Perceived impact on quality of life and efficacy of CAM in glioma patients.** The impact of various CAM categories (A,B alimentation and diet, C,D complementary treatment, E,F alternative treatment) was graded on a numeric analog scale from 0 to 10 (poor to good) and then grouped for graphic representation as 1-3, 4-7 or 8-10, and related to three levels of expenditures per month (less than 50 €, 50-200 €, or more than 200 €).

Figure

Figure 1

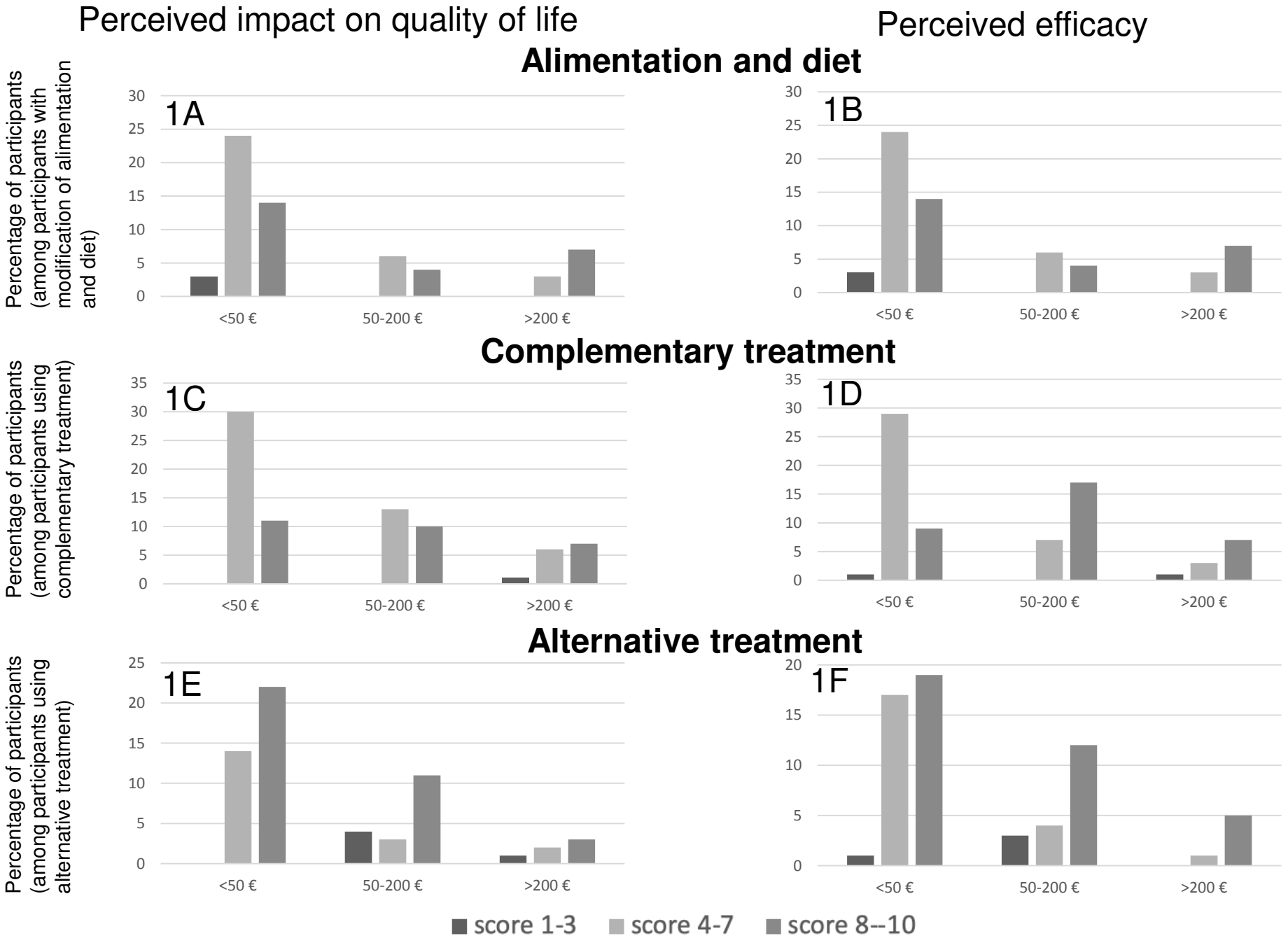

Table 1. Association between patient characteristics and CAM use[1]

	Alimentation and diet	Complementary treatment	Alternative therapy	At least one of these
Gender (women; men) (n=214)	p=0.8845	p=0.5722	p=0.7581	p=0.8863
Age (<35; 34-45; 45-60; >60 years) (n=224)	p=0.8837	p=0.9180	p=0.0811	p=0.3750
Glioma WHO grade (glioblastoma; WHO grade II or III) (n=214)	p=**0.0008**	p=**0.0006**	p=**0.00234**	p=**0.0007**
Recurrence (experienced; not experienced) (n=227)	p=0.2414	p=0.7349	p=0.0971	p=0.5485

[1] Comparative analysis according to gender (women, n=79 versus men, n=135), age (<35, n=51 versus 34-45, n=53 versus 45-60, n=63 versus >60 years, n=57), gliomas WHO grade (glioblastoma, IV, n=105 versus other WHO grades, n=110), and recurrence experienced (recurrent disease, n=102 versus newly diagnosed setting, n=125) were conducted using Chi-square test. A level of significance of 5% was used (significant differences in bold).

Table 2. Smoking, alcohol habits, alimentation and diet

	n (%) or median (minimum-maximum)
Smoking habits	
tobacco (% of participants)	yes: 114 (50%) no:112 (49%) no response: 1 (1%)
- cigarette (% of among tobacco users)	yes: 103 (90%) no: 7 (6%) no response: 4 (3%)
- cigar (% among tobacco users)	yes: 5 (4%) no: 103 (90%) no response: 8 (7%)
- pipe (% among tobacco users)	yes: 2 (1%) no: 106 (93%) no response: 6 (5%)
- active consumption (% among tobacco users)	yes: 57 (50%) no: 49 (43%) no response: 8 (7%)
other* (mainly cannabis) (% of participants)	yes: 32 (14%) no: 151 (66%) no response: 44 (19%)
- active consumption (% among "other" users)	yes: 11 (34%) no: 18 (56%) no response: 3 (9%)
anti-tobacco gum (% of participants)	7 (6%) no:155 (68%) no response: 65 (29%)
modification of smoking habits since the diagnosis (% of participants)	yes: 35 (15%) no: 100 (44%) no response: 92 (40%)
Alcohol consumption (% of participants) no alcohol less than 2 glasses per day between 2 and 4 glasses per day more than 4 glasses per day no response	 56 (25%) 126 (55%) 18 (8%) 1 (<1%) 26 (11%)
Alimentary habits	
- modification of alimentary habits (% of participants)	change: 103 (45%) no change:116 (51%) no response: 8 (3%)

- addition or omission of aliments (% of participants who declared a modification of alimentary habits, n=103)	change: 81 (79%) no change:15 (14.5%) no response: 7 (7%)
Addition of (among patients who declared a modification of alimentary habits, n=103)	
- green tea	yes: 31 (30%) no: 57 (55%) no response: 15 (14%)
- curcuma	yes: 28 (27%) no: 60 (58%) no response: 15 (14%)
- lemon	yes: 27 (26%) no: 61 (59%) no response: 15 (14%)
- broccoli	yes: 23 (22%) no: 64 (62%) no response: 16 (15%)
- carott	yes: 22 (21%) no: 66 (64%) no response: 15 (14%)
- plums	yes: 20 (19%) no: 68 (66%) no response: 15 (14%)
- tomato	yes: 20 (19%) no: 68 (66%) no response: 15 (14%)
- cabbage	yes: 18 (17%) no: 70 (68%) no response: 15 (14%)
- garlic	yes: 18 (17%) no: 70 (68%) no response: 15 (14%)
- onion	yes:16 (7%) no: 72 (70%) no response: 15 (14%)
- nuts	yes: 16 (7%) no: 72 (70%) no response: 15 (14%)

- pomegranate	yes: 14 (13%) no: 74 (72%) no response: 15 (14%)
- sweet potato	yes: 11 (10%) no: 77 (74%) no response: 15 (14%)
- berries	yes: 9 ((9%) no: 79 (77%) no response: 15 (14%)
- chestnut	yes: 8 (7%) no: 80 (78%) no response: 15 (14%)
- other	yes: 56 (4%) no: 34 (33%) no response: 13 (13%)
Diet - diet (% participants)	yes: 27 (12%) no: 189 (83%) no response: 11 (5%)
- ketogenic diet (% among participants under diet, n=27)	yes: 5 (18%) no: 16 (559%) no response: 6 (22%)
- Servent-Scheiber (% among participants under diet, n=27)	yes: 4 (15%) no: 16 (59%) no response: 7 (26%)
- Dukan (% among participants under diet, n=27)	yes: 0 (0%) no: 20 (74%) no response: 7 (26%)
- Khayat (% among participants under diet, n=27)	yes: 0 (0%) no: 20 (74%) no response: 7 (26%)
- other (% among participants under diet, n=27)	yes: 14 (52%) no: 6 (22%) no response: 7 (26%)
Information on alimentation and diet received from (% among participants who declared a modification of alimentary habits or being under diet, n=108)	
- oncologist	14 (13%)
- general practitioner	16 (15%)
- pharmacist	3 (3%)
- nurse at hospital	2 (2%)
- nurse outside of hospital	2 (2%)

- relatives - patient associations - media - other	28 (26%) 3 (3%) 1 (1%) 11 (10%)
Positive impact of modified alimentation on quality of life on a scale from 1 to 10 according to the patient (% among participants who have declared a modification of alimentary habits or being under diet, n=108) Median (interquartile ranges) 1-3 4-7 8-10 no response	 7 (5-9) 5 (5%) 38 (35%) 35 (32%) 30 (28%)
Efficacy of modified alimentation on a scale from 1 to 10 according to the patient (% among participants who have declared a modification of alimentary habits or being under diet, n=108) Median (interquartile ranges) 1-3 4-7 8-10 no response	 7 (5-9) 5 (5%) 42 (39%) 36 (33%) 25 (23%)
Estimation of cost of modified alimentation per month (% among participants who declared a modification of alimentary habits or being under diet, n=108) <30 € 30-50 € 50-100 € 100-200 € 200-500 € >500 € no response	 35 (32%) 7 (6%) 5 (5%) 6 (5%) 9 (8%) 1 (1%) 45 (42%)
Impact of modified alimentation on (% among participants who declared a modification of alimentary habits or being under diet, n=108) - familial organisation - leisures - finances	 yes: 22 (20%) no: 55 (51%) no response: 31 (28%) yes: 12 (11%) no: 66 (61%) no response: 30 (28%) yes: 12 (11%) no: 66 (61%) no response: 30 (28%)

* Among the 15 participants who added a comment, 13 reported using cannabis.

Table 3. Complementary treatment

Any complementary treatment supplement (% of participants)	yes: 100 (44%) no: 124 (55%) no response: 3 (1%)
Vitamins (% of participants)	yes: 52 (23%) no: 172 (76%) no response: 3 (1%)
Food supplement (% of participants)	yes: 51 (22%) no=173 (76%) no response: 3 (1%)
Phytotherapy (% of participants)	yes: 35 (15%) no: 189 (83%) no response: 3 (1%)
Homeopathy (% of participants)	yes: 34 (15%) no: 190 (84%) no response: 3 (1%)
Other medication without prescription (% of participants)	yes: 21 (9%) no: 201 (89%) no response: 5 (2%)
Information received from (% among patients who declared complementary treatment consumption, n=100)* - oncologist - general practitioner - pharmacist - nurse at hospital - nurse outside of hospital - relatives - patient associations - media - other	 15 (15%) 29 (29%) 15 (15%) 4 (4%) 4 (4%) 30 (30%) 4 (4%) 14 (14%) 18 (18%)
Positive impact on quality of life on a scale from 1 to 10 according to the patient (% among patients who declared complementary treatment consumption, n=100)* Median (interquartile ranges) 1-3 4-7 8-10 no response	 7 (5-8) 1 (1%) 55 (55%) 32 (32%) 12 (12%)
Efficacy on a scale from 1 to 10 according to the patient (% among patients who declared complementary treatment consumption, n=100)* Median (interquartile ranges) 1-3 4-7 8-10 no response	 7 (5-8.5) 2 (2%) 40 (40%) 37 (37%) 21 (21%)
Estimation of the cost per month (% among patients who declared complementary treatment consumption, n=100)* <30 €	 38 (38%)

30-50 € 50-100 € 100-200 € 200-500 € >500 € no response	7 (7%) 13 (13%) 11 (11%) 12 (12%) 3 (3%) 16 (16%)
Impact on (% among patients who declared complementary treatment consumption, n=100)*	
- familial organisation	yes: 17 (17%) no: 75 (75%) no response: 8 (8%)
- leisures	yes: 16 (16%) no: 76 (76%) no response: 8 (8%)
- finances	yes: 18 (18%) no: 74 (74%) no response: 8 (8%)

*Only patients who declared a consumption of any complementary treatment were included in the calculation

Table 4. Alternative treatment

Any alternative medicine (% of participants)	yes: 73 (32%) no: 144 (63%) no response: 10 (4%)
Magnetism (% of participants who declared alternative treatment use)	22 (30%)
Acupuncture (% of participants who declared alternative treatment use)	16 (22%)
Sophrology (% of participants who declared alternative treatment use)	15 (21%)
Energizing therapy (% of participants who declared alternative treatment use)	12 (16%)
Aromatherapy (% of participants who declared alternative treatment use)	8 (11%)
Chiropractic (% of participants who declared alternative treatment use)	2 (3%)
Ayurvedic medicine (% of participants who declared alternative treatment use)	2 (3%)
Hypnotherapy (% of participants who declared alternative treatment use)	5 (7%)
Auriculotherapy (% of participants who declared alternative treatment use)	1 (1%)
Other (% of participants who declared alternative treatment use)	21 (29%)
Information received from (% of participants who declared alternative treatment use) - oncologist - general practitioner - pharmacist - nurse at hospital - nurse outside of hospital - relatives - patient associations - media - other	 5 (7%) 5 (7%) 0 (0%) 2 (3%) 2 (3%) 42 (58%) 6 (8%) 55 (75%) 16 (22%)
Positive impact on quality of life on a scale from 1 to 10 according to the patient (% of participants who declared alternative treatment use) Median (interquartile ranges) 1-3 4-7 8-10 no response	 8 (6-9) 3 (4%) 20 (27%) 38 (52%) 9 (12%)
Efficacy on a scale from 1 to 10 according to the patient (% of participants who declared alternative treatment use) Median (interquartile ranges) 1-3 4-7 8-10 No response	 8 (6-9) 3 (4%) 23 (31%) 38 (52%) 9 (12%)
Estimation of the cost per month (% of participants who declared alternative treatment use) <30 €	 22 (30%)

30-50 € 50-100 € 100-200 € 200-500 € >500 € No response	15 (20%) 13 (18%) 7 (10%) 6 (8%) 0 (0%) 10 (14%)
Impact on (% of participants who declared alternative treatment use) - familial organisation - leisures - finances	 yes: 12 (16%) no: 51 (70%) no response: 10 (14%) yes: 5 (7%) no: 58 (79%) no response: 10 (14%) yes: 11 (15%) no: 52 (71%) no response: 10 (14%)